520 Rec'd PCT/PTO 01 OCT 1999

FORM PTO-1390 (REV 11-98) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
9950-0002	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	09/402273
Not Yet Assigned	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/02138	April 3, 1998 (04/03/98)	April 5, 1997 (04/05/97)

TITLE OF INVENTION
ALLERGEN FORMULATION

APPLICANT(S) FOR DO/EO/US
Jorj Terry ULRICH and Alan Worland WHEELER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98. (and Form PTO-1449)
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: Check in the amount of $1,048.00
    Postcard

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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231. (Box PCT)
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(January 1999)

420 Rec'd PCT/PTO 01 OCT 1999

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
Not Yet Assigned 09/14D6273	PCT/EP98/02138	9950-0002

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$970.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$840.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$760.00	
International preliminary examination fee paid to USPTO (37 CFR 1 482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$670.00	
International preliminary examination fee paid to USPTO (37 CFR 1 482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 840.00
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [X] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$ 130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	12 - 20 =	0	X $18.00	$ 0.00
Independent claims	4 - 3 =	1	X $78.00	$ 78.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)	0		+ $260.00	$ 0.00
TOTAL OF ABOVE CALCULATIONS =				$ 1,048.00
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 0.00
SUBTOTAL =				$ 1,048.00
Processing fee of **$130.00** for furnishing the English translation later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00
TOTAL NATIONAL FEE =				$ 1,048.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00
TOTAL FEES ENCLOSED =				$ 1,048.00
			Amount to be: refunded	$
			charged	$

a. [X] A check in the amount of $ 1,048.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 18-0580 . A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Dianne E. REED
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U.S.

Dianne E Reed
SIGNATURE

Dianne E. Reed
NAME

31,292
REGISTRATION NUMBER

"Express Mail" Mailing Label No.: EL 277 205 615 US

Date of Deposit: 01 October 1999

Attorney Docket No. 9950-0002
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
ULRICH et al.

U.S. Serial No.: Unassigned

Group Art Unit: Unassigned

U.S. Filing Date: Herewith

Examiner: Unassigned

International Application No.: PCT/EP98/02138

International Filing Date: 03 April 1998

Title: ALLERGEN FORMULATION

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
BOX PCT
Washington, D.C. 20231

Sir:

This is a preliminary amendment to the patent application identified above. Prior to examination, please enter the amendments indicated below.

AMENDMENTS

IN THE SPECIFICATION:

On page 1, immediately above line 3, please insert the heading:

--Technical Field--.

On page 1, between lines 4 and 5, please insert the heading:

--Background of the Invention--.

On page 1, at line 20, following "GB-A-1 377 074", please insert -- , corresponding to U.S. Patent No. 3,792,159, --.

On page 1, at line 22, following "GB-A-1 492 973", please insert -- , corresponding to U.S. Patent No. 4,070,455, --.

On page 1, at line 23, change "has been" to --is--.

On page 1, at line 27, please replace "GB 2220211 (Ribi)" with --GB-A-2 220 211, corresponding to U.S. Patent No. 4,912,094 and assigned to Ribi Immunochem. Res. ("Ribi")--.

On page 1, at line 30, please replace "Application No. 92/116556" with --Publication No. WO 92/16556--.

On page 1, between lines 31 and 32, please insert the heading:

--Summary of the Invention--.

On page 2, at line 19, please replace "(optionally)" with --optionally--.

On page 2, between lines 24 and 25, i.e., just prior to the paragraph beginning "Typically, the...", please insert the heading:

--Detailed Description of the Invention--.

IN THE CLAIMS:

Please cancel claims 4 and 5 without prejudice.

Also add the following new claims:

--6. (New) A composition according to claim 2, wherein the allergen is coated with the tyrosine.

7. (New) A composition according to claim 2, wherein the allergen is adsorbed onto the tyrosine.

8. (New) A composition according to claim 2, wherein the allergen is coated with and adsorbed onto the tyrosine.

9. (New) A method according to claim 3, wherein the tyrosine, the optionally modified allergen, and the 3-DPML are administered in a single pharmaceutical composition.

10. (New) A method according to claim 9, wherein the allergen is coated with and/or adsorbed onto the tyrosine.

11. (New) A method according to claim 9, wherein the allergen is adsorbed onto the tyrosine.

12. (New) A method according to claim 9, wherein the allergen is coated with and adsorbed onto the tyrosine.

13. (New) A process for preparing an allergen formulation, comprising: (a) mixing an aqueous solution of an allergen with a solution of tyrosine in a strong aqueous acid; (b) neutralizing the mixture of solutions, thereby co-precipitating tyrosine and the allergen; (c) mixing the product of step (b) with 3-DMPL; and optionally (d) adding a physiologically acceptable carrier.

14. (New) A process for preparing an allergen formulation, comprising: (a) modifying an allergen by reaction with a cross-linking agent, to provide a modified allergen; (b) mixing an aqueous solution of the modified allergen with a solution of tyrosine in a strong aqueous acid; (c) neutralizing the mixture of solutions, thereby co-precipitating tyrosine and the modified allergen; (d) mixing the product of step (c) with 3-DMPL; and optionally (e) adding a physiologically acceptable carrier.--

REMARKS

The specification has been amended above in order to (1) insert headings to identify different sections of the patent application, (2) identify U.S. counterparts of cited GB patents, (3) correct a typographical error vis-à-vis PCT Publication No. WO 92/16556, and (4) correct minor informalities. The amendments to the specification add no new matter into the disclosure.

In addition, the claims have been amended above in order to provide clarification and conform the claim language to that normally used in U.S. practice. All claims find support throughout the disclosure, and are in fact drawn from and directly supported by the original claims. Thus, no new matter has been added.

With the above amendments, claims 4 and 5 have been canceled and claims 6-14 have been added. Thus, claims 1-3 and 6-14 are now pending.

The Examiner is welcome to contact the undersigned attorney at (650)851-8501 with any questions concerning this communication.

Respectfully submitted,

10/1/99
Date

By: Dianne E Reed
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F:\Document\9950\0002\Preliminary Amendment 2 wpd

ALLERGEN FORMULATION

This invention relates to novel formulations for use in desensitisation therapy of allergy sufferers.

It is known that desensitisation therapy results in a changed immunological response specific for the allergens administered. Such changes are considered to be responsible for the beneficial effects of the treatment and amelioration of the symptoms of allergy.

The immunological changes responsible for benefit are not entirely understood. Although a raised allergen specific IgG antibody response is considered to be a desirable outcome of therapy, it is now believed that certain changes in the allergen specific T cell (T lymphocyte) response are more important.

Two subclasses of T cell, TH1-like and TH2-like interact with one another via various messenger molecules. In an allergic subject it appears that there is a greater allergen specific TH2 than a TH1 activity. This can lead to a high allergen specific IgE antibody level and greater eosinophil activity. These are two important components of the allergic syndrome.

A change in the above situation to one where there is greater allergen specific TH1 rather than TH2 activity is thought to be an important component of immunotherapy leading to a clinical benefit.

GB-A-1 377 074 describes a process for preparing coprecipitates of tyrosine having an allergen dispersed therein.

GB-A-1 492 973 describes a process for preparing coprecipitates of tyrosine having a modified allergen dispersed therein. The allergen has been modified by treatment with an agent, such as glutaraldehyde, which causes intra-molecular cross-linking and reduces the allergenicity of the product relative to the unmodified allergen.

3 De-O-acylated monophosphoryl lipid A (hereinafter 3-DMPL or "MPL") is known from GB 2220211 (Ribi). Chemically it is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains and is manufactured by Ribi Immunochem Montana. A preferred form of 3 De-O-acylated monophosphoryl lipid A is disclosed in International Patent Application No. 92/116556. 3-DMPL is an example of a substance that can enhance the TH1 over TH2 directing properties of administered allergens.

According to the present invention there is provided a pharmaceutical composition comprising tyrosine, an optionally modified allergen, and 3-DMPL. Typically, the allergen is coated with and /or adsorbed onto tyrosine, for example by co-precipitation or mixing.

The 3-DMPL can be mixed with the other components of the composition prior to administration. Alternatively it can be formulated together with the other components during manufacture of the product. Alternatively, it can be administered at a different site or time

than the other components. Administration can be by a number of routes including parenteral and enteral.

A further aspect of the invention thus provides a method of treating a patient who is susceptible to allergy, which method comprises administering to the said patient an effective amount of tyrosine, an optionally modified allergen, and 3-DMPL.

A further aspect of the invention provides use of tyrosine, an optionally modified allergen, and 3-DMPL, in the preparation of a medicament for use in the prevention or treatment of allergy.

The allergen may be derived from any allergy causing substance, such as a pollen (e.g. ragweed or birch pollen), food, insect venom, mould, animal fur, or house dust mite (*D. farinae* or *D. pteronyssinus*). As used herein, "allergen" includes a mixture of allergens which may be from a single source or more than one source. The term "allergen" also includes peptides containing one or more epitopes of an allergen, such as allergen fragments, prepared by total synthesis, by enzymatic degradation of allergens, or by other means.

The allergen is optionally modified by reaction with a cross-linking agent such as a dialdehyde, more particularly glutaraldehyde.

A further aspect of the invention provides a process for the preparation of a pharmaceutical composition in accordance with the invention, which process comprises (a) (optionally) modifying an allergen by reaction with a cross-linking agent, (b) mixing an aqueous solution of the optionally modified allergen with a solution of tyrosine in a strong aqueous acid, (c) neutralising the mixture of solutions, thereby co-precipitating tyrosine and modified allergen, (d) mixing the product with 3-DMPL, and (e) optionally, adding a physiologically acceptable carrier.

Suitable physiologically acceptable carriers include phenol-saline and sterile water.

Typically, the allergen is modified by treatment with a dialdehyde such as glutaraldehyde, in aqueous solution at a pH of between 5 and 10, typically about 7, and a temperature of between 0 and 100 °C, more usually between 4 and 37 °C, for up to 10 hours, for example about two hours at room temperature. The ratio of allergen to glutaraldehyde is typically in the range 50:1 to 2:1, for example about 10:1.

The intermediate can be freeze dried or used in the next stage.

A solution of the modified allergen, typically at pH 7±1, obtained either as the reaction mixture from the cross-linking process or from the solvation of a solid, is then mixed with a solution of tyrosine in a strong aqueous acid. The strong acid is usually an inorganic acid, preferably hydrochloric acid. The solution of allergen used in this step typically contains between 0.1 µg/ml and 1000 µg/ml allergen protein, for example about 400µg/ml. The ratio of allergen: tyrosine in the mixture is typically in the range $1:4 \times 10^5$ to $1:1 \times 10^2$ w/w.

The resulting mixture of solutions of allergen and tyrosine is neutralised. By neutralisation is meant an adjustment of pH to a value within the range 4.0 to 7.5. It is important that, at no time, or at least at no prolonged time, during the neutralisation does the pH of the solution rise appreciably above 7.5. This condition can be met by vigorous stirring of the solution and by the use only of the required amount of base, if desired. Various buffering agents can usefully be added to the solutions of allergen to assist in pH control during the mixing and neutralising stages.

A particularly useful method of carrying out the neutralisation is for separate streams of the solution of tyrosine in acid and the neutralising base to be run into the solution of allergen. The rates of flow of the added solutions are controlled by pH-state, that is by equipment which regulates the flow of one or both of the solutions so that the pH of the reaction mixture remains substantially constant at a predetermined level. We have found that optimum results are usually obtained by pH control within the range 6.5 to 7.5 though the precise pH may vary according to the nature of the allergen.

The result of the neutralisation is the immediate precipitation of the tyrosine, within and/or upon which the solution of allergen is occluded and/or adsorbed. After the precipitation the mixture is either washed immediately or allowed to stand for a period of from a few hours to a day or two prior to washing.

The resulting precipitate may be removed from the solution by centrifugation or filtration and washed, e.g. with phenol-saline, before being resuspended in a physiologically-acceptable carrier such as phenol-saline, or sterile water, to produce an injectable composition suitable for use in desensitisation therapy in combination with 3-DMPL.

MPL which has been dissolved by the method described in Preparation 3 below or by sonication can be diluted by various means prior to its addition to tyrosine adsorbates of allergens or modifed allergens. The preparation of MPL is initially made at a concentration of typically between 0.5mg per ml and 4 mg per ml, for example 1 mg per ml. It can then be diluted to a concentration of between 500 µg per ml and 20 µg per ml, preferably about 100 µg per ml. This dilution can be made in pure water, or in an aqueous glycerol solution containing between 1% and 4 %, preferably 2 %, glycerol. Such dilutions can then be added to a suspension of the tyrosine adsorbate prepared as described above. For convenience, the concentration of the MPL solution and the tyrosine adsorbate suspension respectively may be selected such that approximately equal volumes of each are admixed to obtain the final product for injection. A typical final product contains about 100µg per ml of allergen and about 250µg per ml of MPL.

The following Example illustrates the present invention:

Preparation 1

A neutral solution of approximately 0.5 mg/ml grass pollen extract which had been partially purified by dialysis or fractionation was chemically modified by the addition of an equal volume of 0.25% w/v glutaraldehyde and the mixture stirred for approximately 2 hours at room temperature. To the above mixture was added phosphate buffer solution at a pH of 7 ±1. The allergen solution was co-precipitated with tyrosine by the simultaneous addition of one volume of L-tyrosine in HCl (prepared by dissolving 24g L-tyrosine to 100ml with 3.8M HCl) and one volume of 3.2M NaOH, to four volumes of allergen solution, with vigorous agitation. The suspension so formed was centrifuged, washed repeatedly with buffered saline to remove contaminants and resuspended to the original volume in buffered saline pH6 ±1.

3-DMPL suitable for coadministration with the above formulation was prepared as described in Preparation 3 below.

Preparation 2

Eight mg of ovalbumin (XOA) were dissolved by mixing in 20ml of EVANS solution. Next 6.9ml of phosphate buffer were added with mixing. The solution was placed in a 100ml beaker containing a magnetic stir bar. While mixing using a magnetic stirrer, 6.9ml of 3.2N NaOH and 6.9ml of 3.8N HCL containing 24% W/V-tyrosine were added simultaneously, dropwise, over a period of 5 min. to form a precipitate. The mixture was allowed to stir for an additional 5 min. and then transferred to a 50ml centrifuge tube and centrifuged for 10 min. at 2500 rpm. After centrifugation the supernatant was decanted and the pelleted precipitate resuspended in 40ml of phosphate buffer. The mixture was centrifuged for 5 min. at 2500 rpm. After centrifugation the supernatant was decanted and the precipitate resuspended in 40ml of phosphate buffer. The mixture was centrifuged for 5 min. at 2500 rpm. After centrifugation the supernatant was decanted and the pelleted precipitate resuspended in 40ml of phosphate buffer saline, pH7.2, containing 0.4% V/V glycerol and 0.01% W/V thimerosal as a preservative. The final product contained approximately 40mg/ml of tyrosine adsorbate. Assuming 100% binding of the XOA to the tyrosine adsorbate the XAO was at 200µg/ml in the final product. The XOA-tyrosine adsorbate was stored at 4°C until needed.

Preparation 3

A 4 mg/ml solution of 1,2-dipalmitoyl-SN-glycero-3-phospho choline (DPPC) in absolute ethanol was prepared. For each 1.0mg of MPL®-TEA salt to be solubilized, 27µl of DPPC were added to dissolve the MPL®. The ethanol was removed by blowing a stream of N_2 gently into the vial. Next 1.0ml of pyrogen-free water for injection was added for each mg of MPL® in the dried MPL® /DPPC mixture. The solution was sonicated in a bath sonicator at 60-70°C until clear. The MPL®/DPPC solution was then filter sterilized by filtration through a SFCA 290-4520 Nalgene 0.2µm filter. The MPL®/DPPC solution was aseptically dispensed at 1.0mg/ml into depyrogenated vials, labelled MPL®-AF, and stored at 4°C.

Biological activity

TH1 inducing activity in mice can be equated with the production of IgG2a and IgG2b antibodies and the TH2 inducing activity with the production of IgG1 antibodies and IgE antibodies.

Therefore, as an example, an experiment was carried out in mice to demonstrate the profiles of the allergen specific antibodies to an exemplar allergen ovalbumen (XOA) which is a well-known food allergen derived from chicken eggs. It was confirmed that a formulation consisting of MPL + XOA+tyrosine stimulated a more advantageous antibody profile than MPL + XOA, XOA+tyrosine or XOA alone.

Groups of 8 BALB/c female mice, 6-8 weeks of age, were injected subcutaneously in the inguinal area with 0.2ml of one of the following vaccines:

XOA+Tyrosine: The XOA tyrosine adsorbate prepared in Preparation 2 above was diluted with an equal volume of phosphate buffered saline within 30 min. prior to injection.

XOA+Tyrosine+MPL: The XOA tyrosine adsorbate prepared in Preparation 2 above was diluted with an equal volume of MPL®-AF at 500µg/ml in phosphate buffered saline within 30 min. prior to injection.

XOA+MPL: XOA was dissolved in phosphate buffered saline at 200µg/ml and diluted with an equal volume of MPL®-AF at 500µg/ml in phosphate buffered saline within 30 min. prior to injection.

XOA Alone: XOA was dissolved at 200µg/ml in phosphate buffered saline and diluted with an equal volume of phosphate buffered saline.

Twenty-one days later the four groups of mice were boosted with 0.2ml of freshly prepared vaccines. Fourteen days following the booster the mice were bled and the sera separated and stored at -70°C until assay.

The sera were assayed by conventional ELISA technique using horseradish conjugated goat anti-mouse IgG_1, IgG_{2a}, and IgG_{2b} antibodies purchased from Southern Biotechnology, Inc. (Birmingham, AL) and used according to the manufacturer's instruction. The IgG_1, IgG_{2a}, and IgG_{2b} titers represent the reciprocal serum dilution giving a reading of >0.1 OD units at A_{490}. The serum IgE levels were measured using an anti-IgE capture ELISA followed by the use of a biotinylated ovalbumin probe. Binding was measured following the addition of a horseradish conjugated strepavidin preparation. The results are reported as OD units at A_{490}.

RESULTS

Formulation	IgG_1 titre	IgG_{2a} titre	IgG_{2b} titre	IgE OD at 1/10 Diltn
XOA + Tyrosine	102400	100	200	0.213
XOA + Tyrosine + MPL	409600	102400	102400	0.104
XOA + MPL	102400	200	400	0.218
XOA alone	6400	<100	<100	0.235
Normal Mouse Serum Values	<100	<100	<100	0.095

Of particular importance is the fact that the combination of allergen + tyrosine + MPL induces less allergen specific IgE antibody than the other combinations. Furthermore, the ratio of IgG2a or IgG2b to IgG1 antibodies is greater and consistent with the highest levels of the two former antibody isotypes seen in the experiment in the mice given allergen+tyrosine+MPL than in any other group of mice. This is indicative of a better ratio of TH1 cell induction over TH2 cell induction in this group compared with that induced in the other groups of mice.

Claims

1. A pharmaceutical composition comprising tyrosine, an optionally modified allergen, and 3-DMPL.

2. A composition according to claim 1, wherein the allergen is coated with and /or adsorbed onto tyrosine.

3. A method of treating a patient who is susceptible to allergy, which method comprises administering to the said patient an effective amount of tyrosine, an optionally modified allergen, and 3-DMPL.

4. Use of tyrosine, an optionally modified allergen, and 3-DMPL, in the preparation of a medicament for use in the prevention or treatment of allergy.

5. A process for the preparation of a pharmaceutical composition according to claim 1 or 2, which process comprises (a) (optionally) modifying an allergen by reaction with a cross-linking agent, (b) mixing an aqueous solution of the optionally modified allergen with a solution of tyrosine in a strong aqueous acid, (c) neutralising the mixture of solutions, thereby co-precipitating tyrosine and modified allergen, (d) mixing the product with 3-DMPL, and (e) optionally, adding a physiologically acceptable carrier.

Please type a plus sign (+) inside this box → [+]

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	9950-0002
First Named Inventor	ULRICH, Jorj Terry
COMPLETE IF KNOWN	
Application Number	09/402,273
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ALLERGEN FORMULATION

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 04/03/1998 as United States Application Number or PCT International Application Number PCT/EP98/02138 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
9706957.9	United Kingdom	April 5, 1997 (04/05/1997)	☐	☐	☒
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ *Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:*

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
		☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/EP98/02138	April 3, 1998 (04/03/98)	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*
OR
☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
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HARTRUM, J. Elin	43,663	WU, Louis L.	44,413
WILSON, Mark A.	43,275		

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
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Inventor's Signature	Jorj Terry Ulrich					Date	
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☒ Additional Inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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PTO/SB/02A (3-97)
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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 1

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